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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,372	04/19/2006	Mara Rossi	SER-107	9428

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EXAMINER	
DANG, IAN D	
ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
11/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/576,372	ROSSI ET AL.	
	Examiner	Art Unit	
	IAN DANG	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-25,32-34,38-46,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-25,32-34,38-46,48,49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Upon further consideration of Applicant's arguments and Examiner's previous rejections, the Examiner has determined that the finality of this application needs to be withdrawn. Therefore, the finality of the previous office action has been withdrawn and prosecution on the merits continues. The final action was mailed 07/06/2009.

Although the Examiner indicated that claims 22-25, 32-34, 38-46, 48, and 49 are allowable in the Office action mailed 07/06/2009, the Examiner has reconsidered the allowability status of these claims based on further review of the prior arts used in the rejections made in the previous office actions mailed 04/30/2008, 01/22/2009, and 07/06/2009.

Status of Application, Amendments and/or Claims

The amendment of 06 October 2009 has been entered in full. Claims 1-21, 26-31, 35-37, and 47 have been cancelled and claim 41 has been amended.

Claims 22-25, 32-34, 38-46, 48, and 49 are under examination.

Claim Objections

The objection made to claim 41 has been withdrawn in view of the amendments made to claim 41. Claim 41 now defines the acronym "TMAE" with "trimethylaminoethyl-derivatized" and then placed the acronym in parenthesis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
This application currently names joint inventors.

In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-25, 32-34, 38-46, 48, and 49 are drawn to a process for the production of purified interleukin-18 binding protein (IL-18BP) comprising loading a fluid selected from urine or cell culture supernatant and containing IL-18BP onto a hydrophobic charge-induction chromatography resin equilibrated to a pH of 6.1 +/1 0.1 with a buffer and eluting the IL-18BP from said hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4+/1 0.1. or pH of 9.1±0.2 .

Claims 22-25, 32-34, 38-46 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Boschetti E. (2002, TRENDS in Biotechnology, Volume 20, Issue 8, pages 333-337) in view of Xiang et al. (2001, The Journal of Biological Chemistry, Volume 276, Issue 20, pages 17380-17386) and Burton et al. (1998, Journal of Chromatography A, Volume 814, pages 71-81).

Boschetti E. (2002, TRENDS in Biotechnology, Volume 20, Issue 8, pages 333-337) teaches that hydrophobic charge induction chromatography (HCIC) using 4-mercapto-ethyl-pyridine as the ligand is an effective method for the separation of antibodies from a variety of

feedstocks (page 333, abstract). In addition, Boschetti E. teaches that to reach the high purity required for therapeutic applications, the combination of two or more chromatographic procedures is necessary (page 336, right column 3rd full paragraph). Moreover, Boschetti E. teaches that the aim of the first capture step is to selectively adsorb antibodies (page 336, right column 3rd full paragraph). Furthermore, Boschetti E. teaches that several suggestions can be formulated for the use of HCIC in combination with complementary separation techniques, such as the combination of HCIC with anion exchange or with hydroxyapatite chromatography (page 336, right column 3rd full paragraph). Finally, Boschetti E. teaches that cation exchange capture step be followed by HCIC (page 336, right column, end of 3rd full paragraph). However, Boschetti does not teach a process for the purification of IL-18BP and the equilibration to pH of 6.1 +/- 0.1 with a buffer of a hydrophobic charge-induction chromatography resin and elution the IL-18BP from the hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4 +/- 0.1.

Xiang et al. (2001, The Journal of Biological Chemistry, Volume 276, Issue 20, pages 17380-17386) teach that mature human IL-18BP resembles significantly an immunoglobulin (Ig) domain that includes a highly conserved pair of cysteines and tryptophan residues (page 17380, right column, 1st full paragraph). In addition, Xiang et al. teach that IL-18BP was purified from cell culture supernatant (page 17381, left column 2nd full paragraph).

In addition, the reference by Burton describes that hydrophobic charge induction chromatography can be used for the purification of proteins, such as chymosin, chymotrypsinogen, and lysozyme, by varying the pH of the buffers used for their purification independent of the ionic strength of the buffers. More specifically, the reference by Burton recites adsorption and elution of proteins using hydrophobic charge induction chromatography could be carried out within the pH 5-9 range (Page 71, abstract). The range of pH recited by

Burton includes the pH of 6.1 +/- 0.1, 8.4 +/- 0.1, or 9.1 that are required for the purification of IL-18BP using hydrophobic charge induction chromatography in the claimed invention

The teachings of Boschetti (2002), Xiang (2001), and Burton (1998) have been disclosed at pages 3-6 of the office action mailed 01/22/2009 and at pages 8-9 of the Office action mailed 10/09/2007. It can be concluded that the references of Boschetti, Xiang, and Burton while contributing towards the claimed invention do not specifically teach a hydrophobic charge-induction chromatography equilibrated to a pH of 6.1 +/ 0.1 with a buffer and elution the IL-18BP from said hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4+/1 0.1 or 9.1.

Under *KSR*, it's now apparent "obvious to try" may be an appropriate test in more situations than we previously contemplated. When there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try may show that it was obvious under § 103 (*KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007)).

With the combined teachings of Boschetti, Xiang, Burton, and the general knowledge of skill in the art, it would have been obvious for one skilled in the art to specifically develop a process for the production of purified interleukin-18 binding protein (IL-18BP) comprising loading a fluid selected from urine or cell culture supernatant and containing IL-18BP onto a hydrophobic charge-induction chromatography resin, eluting the IL-18BP from said hydrophobic charge-induction chromatography resin equilibrated to a pH of 6.1 +/1 0.1 with a buffer and eluting the IL-18BP from said hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4+/1 0.1.

In addition, it would have been obvious for one skilled in the art to modify the process for the production of purified interleukin-18 binding protein (IL-18BP) as taught by Boschetti, Xiang,

and equilibrated to a pH of 6.1 +/1 0.1 with a buffer and eluting the IL-18BP from said hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4+/1 0.1 because "a person of ordinary skill has good reason to pursue the known options within is or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."

In addition, one of skill in the art would have been motivated to add one or more ultrafiltration steps to the purification process of IL-18BP because the additional purification step would increase the purity of IL-18BP ,effectiveness and the biological activity of the purified IL-18 BP.

In response to the above rejection, at pages 7 and 8 of the response filed 04/21/2009, Applicants indicate that in the reference by Boschetti, the MEP column is loaded at a pH of 8.5 and the desorption of antibodies is carried out at a pH of 4.0 (see legend to Fig. 2 and the paragraph bridging pages 333-334). Burton et al. also teach desorption of proteins using acidic pH (see, for example, page 74, section 2.4 (teaching desorption of chymosin at a pH of 2) and page 79, section 3.5 (teaching the use of a pH of 5-5.5 for elution of proteins on various pyridyl matrices)). Thus, it is clear that the limitations of the rejected claims are not taught by the combined teachings of Boschetti and Burton et al. and that a prima facie case of obviousness for the claimed invention has not been established.

Additionally, Applicants allege that modifying the teachings of Burton et al. and Boschetti et al. such that columns are loaded at an acidic pH and desorbed at a basic pH would render the methods of the prior art unsuitable for their intended purposes (namely the purification of proteins via elution using a pH gradient that becomes more acidic). Specifically (and as discussed above), both Boschetti and Burton et al. teach that proteins are desorbed from MEP columns by acidic pH.

Applicants' arguments and response have been considered but are not persuasive. Although the references by Boschetti and Burton teach the desorption of proteins is performed using acidic pH, these references disclose the desorption of specific proteins: Boschetti

indicates an acidic pH for the desorption for an antibody and the reference by Burton indicates an acidic pH for the desorption of chymosin. However, the issue regarding the desorption of proteins is not relevant to claim 22, since the conditions recited in the two references are specific to an antibody and chymosin that have distinct purification requirements from the ones needed for the purification of IL-18BP. The recitation claim 22 that includes the equilibration to pH of 6.1 +/- 0.1 with a buffer of a hydrophobic charge-induction chromatography resin and elution the IL-18BP from the hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4 +/- 0.1 are specific to IL-18BP and may not be applicable to other proteins.

Moreover, although the reference by Burton does not specifically teach a hydrophobic charge-induction chromatography resin equilibrated to pH of 6.1 +/- 0.1 with a buffer and eluting the IL-18BP from the hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4 +/- 0.1 as recited in claim 22, the hydrophobic charge-induction chromatography resin equilibrated to pH of 6.1 +/- 0.1 with a buffer and eluting the IL-18BP from the hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4 +/- 0.1 as recited in claim 22 would be obvious to one skilled in the art in view of the reference by Burton teaching adsorption and elution could be carried out within the pH 5-9 range (Page 71, abstract) and through routine optimization. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In addition, it would have been obvious for one skilled in the art to modify the process for the production of purified interleukin-18 binding protein (IL-18BP) as taught by the combination of the teachings of Boschetti, Xiang, and Burton by a hydrophobic charge-induction chromatography resin equilibrated to pH of 6.1 +/- 0.1 with a buffer and eluting the IL-18BP from the hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4 +/- 0.1.

One of ordinary skill in the art at the time the invention was made would have been motivated to optimize the pH for the purification of IL-18BP with a hydrophobic charge-induction chromatography resin equilibrated to pH of 6.1 +/- 0.1 with a buffer and eluting the IL-18BP from the hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4 +/- 0.1 from the teachings of Burton reciting adsorption and elution could be carried out within the pH 5-9 range (Page 71, abstract) because the optimal pH for the equilibration of the HCIC resin and for the elution of IL-18BP can be easily performed by trial and error by experimentation with different pH conditions within the range of 5-9.

Finally, one of ordinary skill in the art at the time the invention was made would have been motivated to optimize the pH for the purification of IL-18BP with a hydrophobic charge-induction chromatography resin equilibrated to pH of 6.1 +/- 0.1 with a buffer and eluting the IL-18BP from the hydrophobic charge-induction chromatography resin with a buffer having a pH of 8.4 +/- 0.1 because "a person of ordinary skill has good reason to pursue the know options within is or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."

At pages 7 and 8 of the response filed 10/30/2008, Applicants argue that the cited reference does not teach that this segment of the mature IL- 18BP is an Ig domain; rather, 60% of human IL- 18BP resembles an Ig domain. Further, applicants argue that the cited reference indicates that the predicted Ig domain of IL-18BP has only about 25% amino acid sequence identity with a similar domain within the IL-1 receptor (page 17380, column 2, first full paragraph) and the cited teaching provides no guidance as to the degree of similarity the IL-18BP has with immunoglobulin molecules or domains thereof. Thus, it is unclear that one skilled in the art would have had a reasonable expectation of success in purifying IL-18BP or that one skilled in the art would have been motivated to utilize hydrophobic charge induction chromatography, on the basis of the cited references, because the similarity of IL-18BP to an immunoglobulin or immunoglobulin domain is unclear.

Applicants' arguments and response have been considered but are not persuasive. Although Applicants indicate that the similarity of IL-1BP to an immunoglobulin or immunoglobulin domain is unclear, Applicants have not provided any scientific evidence that the teachings by Xiang reciting "60% of human IL-18BP resembles an Ig domain" is not sufficient for the purification of IL-18BP using hydrophobic charge-induction chromatography. Such an argument therefore appears to be just an opinion of the applicant than scientific evidence. Applicants do not provide any scientific evidence that the 60% resemblance of human IL18BP is not enough for concluding that the technique used for purifying the antibody can be applied to purify a protein that resembles an antibody or that one of skill in the art would not be motivated to use the HCIC technique for purifying IL-18BP. In the absence of such scientific evidence, the resemblance of IL-18BP to an Ig domain as recited by the reference by Xiang is sufficient motivation for one of skill in the art of purify IL-18 BP with hydrophobic charge-induction chromatography based on the teachings of Boschetti.

Finally, the reference by Xiang et al. discloses that IL-18BP has structural characteristics that are similar to an immunoglobulin IgG by reciting "that approximately 60% of the mature human IL-18BP resembles an immunoglobulin (IgG) domain that includes a highly conserved pair of cysteines and tryptophan residues" and by comparing it to another protein with similarities to immunoglobulin such as only about 25% amino acid sequence identity with a similar domain within the IL-1 receptor. Xiang et al. recite that the resemblance to IL-18BP is appropriate because IL-18 itself is not an immunoglobulin because the structural similarities of IL-18BP to an IgG disclosed by Xiang et al. can be utilized to purify it with methods used for the purification of immunoglobulin.

Accordingly, the invention taken as a whole is *prima facie* obvious.

Conclusion

No claim is allowed.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IAN DANG whose telephone number is (571)272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Patent Examiner
Art Unit 1647
November 2nd, 2009

/Manjunath N. Rao /
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